National Journal of Physiology, Pharmacy and Pharmacology

REVIEW ARTICLE

Orexin system increases energy expenditure by brown adipose tissue activity

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Received: February 28, 2017; **Accepted:** April 22, 2017

ABSTRACT

Adipose tissue is a biological caloric reservoir that expands itself in response to overnutrition and releases lipids in response to energy deficit. It comprises white adipose tissue, the main energy storage, and brown adipose tissue (BAT), a key site of thermogenesis that dissipates chemical energy as heat. BAT is richly innervated by sympathetic nerve efferent fibers, and its development and activation are mediated by the sympathetic nervous system (SNS). Furthermore, substantial evidences show that BAT activation leads to increased thermogenesis. Thus, the regulation of the SNS tone provides a complex mechanism able to specifically coordinate the function of the organs involved in energy homeostasis. On the other hand, adipose tissue acts as an endocrine organ by producing various signaling cytokines and interacting with some neuropeptides as orexins. Orexins are produced by the lateral hypothalamus and evidences have suggested that orexins promote energy expenditure (EE) through modulation of locomotor activity and BAT thermogenesis. Recent data also suggest that orexins are required for BAT development, differentiation, and function. In the light of this, the orexin neuropeptides are part of a network able to increase EE through modulation of BAT thermogenesis which can be a target to new strategies to reduce the incidences of overweight and obesity. Aim of this review is to report our evidences showing that the autonomic nervous system influences food intake and energy consumption under various conditions, such as injection of orexins, which change the sympathetic and/or parasympathetic activities.

KEY WORDS: Adipose Tissue; Orexin; Autonomic Nervous System; Thermogenesis; Eating Behavior

INTRODUCTION

Adipose tissue, or fat, is an anatomical term for loose connective tissue composed of adipocytes; it is a biological caloric reservoir that expands in response to overnutrition, storing excess calories as triglycerides in adipocytes lipid droplets, and releases lipids in response to energy deficit.[1,2] This unparalleled capacity links the cell biology of the adipocyte and adipose tissue physiology to whole body metabolism. Adipocytes exist in a spectrum of subtypes, identified by color, from white to brown. White adipocytes constitute the classical fat cell representing the majority of cells in visceral and subcutaneous adipose depots. Brown adipocytes encompass smaller brown fat depots that play a role in thermogenesis in most mammalian species.[1,3]

Access this article online	
Website: www.njppp.com	Quick Response code
DOI: 10.5455/njppp.2017.7.0205422042017	

Therefore, the adipose organ comprises white adipose tissue (WAT), the main energy storage allowing animals to survive for longer periods without meals, and brown adipose tissue (BAT), a key site of heat production (thermogenesis) in mammals, essential for the survival in cold environments and in hibernators, defending core body temperature.[3] Brown fat cells possess numerous mitochondria that contain a unique protein called uncoupling protein 1 (UCP1). UCP1 dissipates the proton motive force that is normally used to drive the synthesis of cellular adenosine triphosphate (ATP), releasing the energy in the mitochondrial electrochemical gradient in the form of heat.[4,5] Besides, brown adipocytes are richly innervated by sympathetic nerve efferent fibers, which ensure Central Control of thermogenesis and BAT is highly vascularized to allow the dissipation of generated heat.[5-7] UCP1 cells can also accumulate in small pockets in white fat depots, especially in the subcutaneous adipose tissues, particularly when mice was exposed to long-term cold or stimuli with hormones such as catecholamines and other b-adrenergic agonists.[7] This adaptive thermogenesis is robustly activated by cold via an indirect pathway mediated by the sympathetic nervous system (SNS). However, despite these similarities, it is now clear that the "classical" brown fat cells and the inducible "beige" fat cells come from different developmental lineages and are, in fact, distinct cell types.[3,8]

The regulation of the SNS tone provides a complex mechanism able to coordinate the function and crosstalk of the organs involved in energy homeostasis.[5]

The adaptive thermogenic response to cold and high-fat diet increases the SNS outflow to BAT, the different lipolytic requirements of these two conditions are met by the increase or decrease of the sympathetic outflow to selected WAT depots showing an organ selectivity of the SNS.[9] During caloric restriction, there is a decrease in SNS outflow to BAT resulting in reduced energy expenditure (EE), and simultaneous increase in SNS outflow to specific WAT depots to facilitate lipid mobilization. However, in obese patients, regulation of the SNS outflow seems to be more widespread and more complex than in non-obese subjects, preferentially affecting heart, kidneys, muscle, and vascular wall, and triggering the development of cardiovascular complications.[10] The key points are that regulation of the SNS allows specific responses to specific physiological conditions and that the adaptive SNS response to cold promotes thermogenesis by targeting BAT and is devoid of undesirable cardiovascular effects. Substantial evidences show that BAT activation leads to increased thermogenesis potentially useful to prevent or reverse obesity and diabetes in multiple experimental models. Besides, in central obesity there is an elevated sympathetic outflow to organs such as the heart, kidneys, and blood vessels that can also contribute to a further decline of insulin sensitivity, creating a vicious cycle which concurs to metabolic syndrome and hypertension development. The cause of this overactivity is not clear but may be driven by certain adipokines, signaling cytokines produced by adipose tissue (including orexin, leptin, free fatty acids, tumor necrosis factor, interleukin-6, C-reactive protein, angiotensinogen, and adiponectin).[11,12] Furthermore, the postprandial activation of the peripheral SNS is crucial to maintain energy balance. Signals related to food intake from various origins (e.g., gut, hepatoportal area, and baroreceptors) are integrated in the brain and increase peripheral sympathetic outflow. This activation depends on the size and composition of the meal, and diet composition has a key role in the sympathetic activation level during the day in view of the potential role of adrenergic overactivity in the pathogenesis of obesity and its metabolic syndrome.[13,14]

Therefore, energy homeostasis is a balance between caloric intake and EE regulated by interconnected neuroendocrine and autonomic pathways.[10]

Energy homeostasis is also regulated by the hypothalamus, which continuously monitors signals that reflect energy status and initiates appropriate behavioral and metabolic responses.[15]

Neurons located in the lateral hypothalamic (LH) area, the dorsomedial nucleus of the hypothalamus and perifornical hypothalamus produce orexins (OX-A and OX-B), also named hypocretins.[16,17] Compelling evidence derived from genetic mouse models has suggested that orexins promote EE through modulation of locomotor activity and BAT thermogenesis.[18-20] Recent data also suggest that orexins are required for BAT development, differentiation, and function and, orexin knockout mice are prone to diet-induced obesity since the lack of orexin's action compromises energy balance.[21] In the light of this, BAT-induced thermogenesis is potentially a useful antiobesity strategy. Investigation into the mechanisms that control body weight and the fat mass (FM) gives growing relevance to the possibilities of new strategies to reduce the incidences of overweight and obesity, which are frequently associated with metabolic and cardiovascular diseases.

However, in order for this to become viable, given the scarcity of BAT in humans, it is essential to optimize the development and activation of BAT. Physiologically, the development and activation of BAT involve adrenergic stimulation mediated through the SNS. This vision should modify the interpretations about the sympathetic function in the pathophysiology of obesity. However, this causes problems, as it is difficult to specifically target SNS activation of BAT. Potential approaches to solve this problem include targeting the SNS at a central level; however, this presents huge challenges, given the complexity and promiscuity of the neuronal networks.[5]

This review reports our evidences showing that the autonomic nervous system controls body weight and FM by influencing

food intake and energy consumption. The general research project was to test the influence of the autonomic nervous system on energy balance under various conditions, which change the sympathetic and/or parasympathetic activities.

EXPERIMENTAL EVIDENCES

Animal Studies

First experiment

This experiment tests the effect of intracerebroventricular (ICV) injection of prostaglandin E1 (PGE_1) on: 1) sympathetic activity and body temperature; 2) food intake. The firing rate of the sympathetic nerves to interscapular BAT (IBAT), along with IBAT and colonic temperatures (T_{IBAT} and T_C) were monitored in male Sprague-Dawley rats before and 90 min after food presentation. The IBAT is the organ responsible for evoking 35-65% of the total increase in metabolic heat production unrelated to shivering during experimental manipulations in rodents.[22] An ICV injection of PGE_1 (500 ng) or saline was given immediately before food presentation. The amount of food ingested was also measured. The upper panel of Figure 1a illustrates cumulative curves of food intake. PGE_1 reduces the ingestion of food. Middle-upper panel shows the percentage changes in firing rate of nerves to IBAT. The increase was higher in the animals with PGE_1 injection. Middle-lower and lower panels illustrate T_{IBAT} and T_C changes. The elevation of body temperature was higher in the animals with PGE_1 injection.[23] Therefore, PGE_1 induces a higher elevation of body temperature and a reduction of food intake. This study demonstrated that during an intracerebroventricular injection of PGE_1 body temperature increase was inversely proportional to food intake suggesting that PGE_1 controls both sympathetic activation (and related body temperature elevation) and food intake.[24] In this study, the increase in body temperature due to PGE_1 can be recognized as a satiety signal, which reduces food intake.[24] The preoptic area/anterior hypothalamus (PO/AH) is a responsive structure to PGE_1, whereas this neural mediator slightly stimulates the other hypothalamic areas. This data suggests that PGE_1 injected into a cerebral ventricle acts on the PO/AH, which in turn, could influence the ventromedial hypothalamus (VMH), a key structure in the control of sympathetic activity and food intake.[24-26] This view is in agreement with our previous experiment showing that a VMH lesion reduces both sympathetic and thermogenic responses after PGE_1 injection.[27]

Second experiment

In this study, we investigated the effect of the thermogenic activation induced by orexin A on eating behavior. Food intake, T_{IBAT} and abdominal temperatures (T_{ab}) were monitored in 24 h-fasting male Sprague-Dawley rats for 12 h after food presentation. Orexin A was injected (1.5 nmol) into the lateral cerebral ventricle 6 h before food presentation. During the same period, T_{IBAT} and T_{ab} were also monitored. The same variables were analyzed in rats receiving orexin A contemporaneously to food presentation. Figure 1b illustrates cumulative food intake, T_{IBAT} and T_{ab}. The rats receiving orexin 6 h before food presentation showed a reduction in food intake with respect to other animals. The effects of orexin A on food intake depends on body temperature at the time of food presentation.[28] Our results underline the importance of orexin A in the control of body temperature, which, in turn, affects eating behavior. In this experiment, an ICV injection of orexin A induces an increase in the sympathetic activity and in the T_{IBAT} independently of food ingestion, which is reduced in the rats with a delayed presentation of food. Moreover, the effects of orexin A on body temperature are predominant with respect to food intake.[29] Therefore, orexin A can induce not only an increase but also a decrease in food intake, as in this experiment, however, it always induces an activation of thermogenesis. We can suppose that this peptide elevates the thermal set point, triggering the reactions that help body temperature to reach a new level. Indeed, food ingestion induces a rise in body temperature due to postprandial thermogenesis.[28] The hyperphagic effect of orexin A disappears when the body temperature is already increased, such that a reduction in food intake can happen in this condition.

Orexin A affects the temperature of IBAT, which is the most important effector of nonshivering thermogenesis in the rat,[14,30,31] illustrating that the rise in heat production is also due to the thermogenesis activation unrelated to muscle activity. This confirms the role of the SNS on IBAT activity. The increase in (T_{ab}) emphasizes the effect of orexin A on "core" temperature suggesting the inclusion of orexin A among the peptides that control body temperature.

Given the influence of orexin A in thermoregulation, it is appropriate to control the eating behavior.[32-34] Although these experiments could be repeated with an antagonist of the orexin receptors and/or a blocker of the sympathetic activity, these findings well demonstrated the possibility that orexin A can induce hypophagia.[35,36]

Human Studies

Vegetative modulation, expressed as power spectral analysis of heart rate variability (HRV), was investigated in lean and obese women at premenopausal or postmenopausal age.[34] The HRV power spectrum was evaluated on a 5-min long electrocardiogram recording. To estimate the sympathetic and parasympathetic activities, the absolute values of the spectrum were summed in the following frequencies used: A low frequency (0.04-0.15Hz; LF) and a high frequency (0.15-0.40; HF) range. The LF and HF in premenopausal obese women were lower than in lean women, and this decrease was also found in postmenopausal

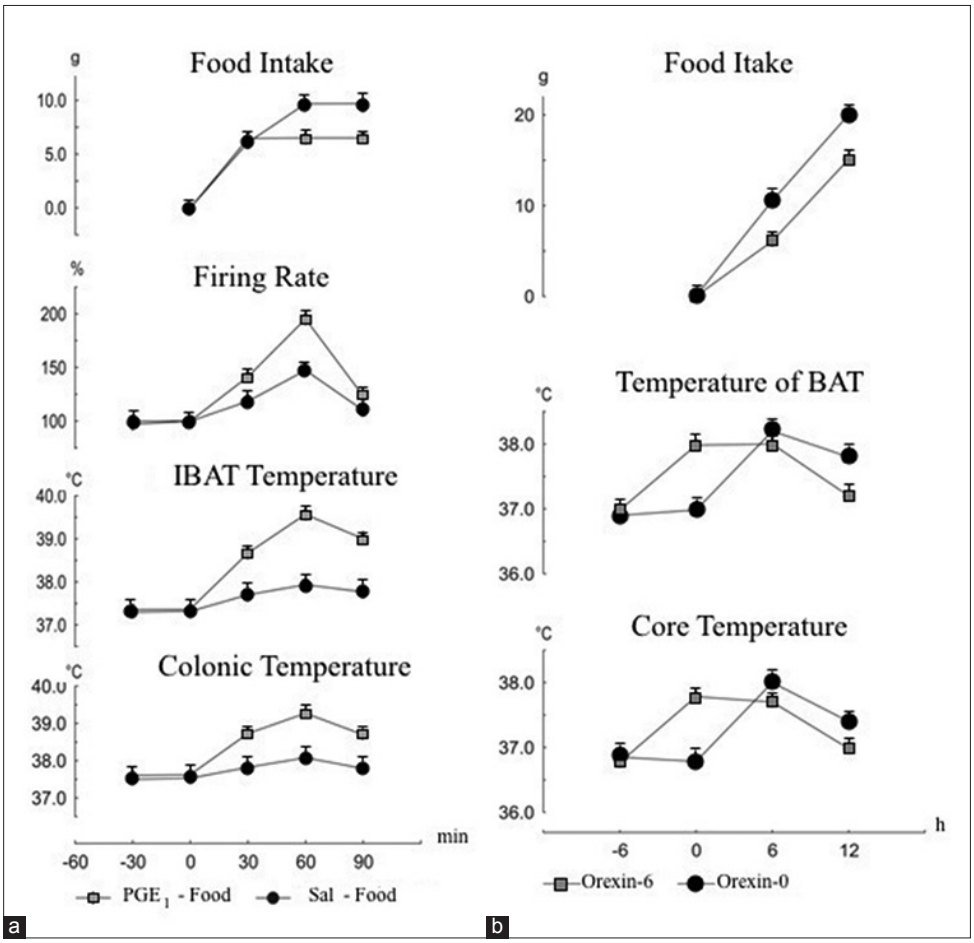

Figure 1: (a) Cumulative values of food intake (upper panel), changes in firing rate (middle-upper panel), changes in temperature of interscapular brown adipose tissue (IBAT) (middle-lower panel) and changes in colonic temperature in the rats with prostaglandin E_1 or saline injection (lower panel). Injection and food presentation at time 0, (b) Cumulative food intake, IBAT and core temperatures. Food presentation at time 0. Orexin was injected 6 h before food presentation (−6) or contemporaneously to food presentation (0). Values are expressed as a mean ± standard error

obese women.[37,38] These findings indicate a reduced vegetative modulation in obese women and the reduction of the autonomic control with regard to both the sympathetic and parasympathetic components.[39,40] The reduction of the sympathetic branch could be an important factor in the maintenance of obesity in premenopausal age due to a low EE explaining the higher body weight in premenopausal women. This vision is in accordance with the "Mona Lisa hypothesis" an acronym for "most obesities known are low in sympathetic activity."[39,41] In this experiment, the autonomic activity of postmenopausal women is lower than that in premenopausal women indicating that changes in the autonomic modulation cannot be included among factors related to obesity in postmenopausal subjects.[39] Furthermore, considering that an increase in sympathetic and thermogenic activity reduces food intake, obesity can be due to an increase in food intake associated to a reduced activity of the SNS. On the other hand, the evaluation of cardiorespiratory interactions, in particular, the HRV, can provide diagnostic information about early subclinical autonomic dysfunction in obesity. Lower respiratory sinus arrhythmia, evaluated by the HF-HRV spectral analysis combined with deep breathing tests, reveals the presence of cardiac vagal dysfunction in obese adolescents.[38] Importantly, autonomic imbalance with decreased parasympathetic activity maybe the final common pathway in numerous conditions associated with increased morbidity and mortality.[38,42]

Changes in the autonomic nervous system activity and in resting EE (REE) can also be induced by sports.[41,43-46] Physical activity enhances the parasympathetic tone, and a reduced heart rate (induced by vagal influence) is considered as an index of training status in athletes.[43,47,48] Since few studies compare vegetative and energetic changes of sedentary and sportive subjects. The influence exerted by sedentary and basketball exercise training on the relationship between the activity of the autonomic nervous system, REE and body composition was evaluated.[49-51] The physical activity induced an increase in REE and free FM without variations in body weight and basketball players showed a significant increased parasympathetic activity, measured by the prostate-specific antigen (PSA) of HRV.[52,53] These findings demonstrate that REE is higher in the athletes than in sedentary women, despite the augmented parasympathetic

activity, usually related to lower EE.[44,54] This is the first study to examine the effect of long-term training on relationship among cardiac HRV, REE, and body composition. In this study, an increase in the HF of the HRV-PSA has been noted in sportive women, confirming that exercise induces an increase in the parasympathetic activity at resting. On the contrary, the LF of the PSA of HRV was not modified by sport activity, indicating that basketball does not modify the sympathetic discharge. The increase in the parasympathetic activity is associated with an increase in REE.[55-57] This result is important considering that the parasympathetic activity has generally been demonstrated to have an inverse relationship with REE.[44,58]

DISCUSSION

The above-reported evidences indicate that the autonomic nervous system can be considered a fundamental factor in the regulation of food intake and body weight. The ability to modulate energy intake and expenditure according to environmental conditions is the key to ensuring the survival of an organism. Multiple neuropeptides can modulate energy balance through different mechanisms, including control of food intake, thermogenic activity, sympathetic modulation, control of voluntary, and spontaneous physical activity.[59] As discussed in this review, the orexin neuropeptides are part of this network affecting energy balance through modulation of EE and intake. Orexins can increase EE by modulating BAT thermogenesis.[19] In BAT, UCP proteins uncouples ATP production from mitochondrial respiration dissipating energy as heat.[30] Higher activity of UCP proteins determines the lower efficiency of energy metabolism and resistance to body weight gain. Sellayah et al. demonstrated that orexin is required for normal development of BAT effecting directly on differentiation of new brown adipocytes, and orexin knockout mice gain more weight on a high-fat diet compared to wild-type mice.[21]

Furthermore, many of the brain locations for WAT including the paraventricular nucleus (PVN) of the hypothalamus (PVN), LH and nucleus of the solitary tract, are also involved in BAT regulation.[59,60] Recently, Messina et al.[31] have identified an important role for central orexin in BAT regulation via the SNS.

A direct orexigenic projection from LH to raphe pallidus activates its efferents to premotor sympathetic neurons in the spinal intermediolateral nucleus.[31] Orexin A injection in the dorsal raphe and parapyramidal area increased the thermogenic activity of BAT and CO_2 release in anesthetized rats.[60] Thus, orexins can increase sympathetic outflow to BAT increasing its thermogenic activity. Although the mechanisms by which the orexins can promote EE are not clear, the evidence reviewed here suggests that, when physical activity increases, the orexins can promote WAT lipolysis and BAT thermogenesis, both being consistent with a net effect of orexins to increase EE.[21]

PERSPECTIVES

BAT is now accepted as a regulatory site of (EE) and body fatness in adult humans. Moreover, other studies have indicated that BAT has roles in the regulation of glucose and lipid metabolism through somebody fat-independent mechanisms. These findings collectively suggest that BAT may also be involved in the etiology of glucose intolerance, and/or of obesity. Thus, BAT is a promising target for combating not only obesity but also some related metabolic diseases.

CONCLUSION

BAT is a strategic organ in the control of the temperature through heat dissipation. Recent developments have demonstrated that "traditional" hormones such as thyroid hormones, estradiol and also orexin modulate the BAT function by acting on several hypothalamic nuclei. However, although the recent developments in this field have generated a lot of excitement, some doubt still exists with regard to the possibility of targeting BAT thermogenesis as a mechanism to treat obesity. In addition, work will be needed to demonstrate if controlling thermogenesis will be of valuable clinical therapeutic application in the future.

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How to cite this article: Messina A, Monda V, Villano I, Valenzano AA, Salerno M, Tafuri D, et al. Orexin system increases energy expenditure by brown adipose tissue activity. Natl J Physiol Pharm Pharmacol 2017;7(7):658-664.

Source of Support: Nil, **Conflict of Interest:** None declared.